Biosecurity and Health

Science and technology designed to battle pathogens

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Harshini Mukundan (left) watches as fellow Los Alamos bioscientist Elizabeth Hong-Geller loads a vertical electrophoresis gel, used to separate proteins and small molecules. This technique is useful for developing improved methods to detect pathogens.
Overview of Research and Highlights

Los Alamos scientists are developing science and technology to improve pathogen detection, create better therapeutics, and anticipate—even prevent—epidemics and pandemics.

The source of these pathogens can be natural (for example, a mosquito that carries the West Nile Virus) or manmade (for example, the 2001 Anthrax letters).

LANL contributions to this area of research include understanding the host-pathogen relationship, creating better detection platforms, modeling disease progression, and developing strategies for more effective drugs.

Regardless of the origin—natural or man-made—limiting the impact of disease requires rapid identification of disease and an effective, targeted response. LANL scientists are contributing to this effort in many areas, including:

- Understanding the molecular mechanisms of host-pathogen interactions.
- Discovering new biomarkers of disease.
- Developing effective recognition molecules for detection reagents—both RNA and protein.
- Developing effective vaccines and therapeutics.
- Designing advanced diagnostic assays and biosensors for rapid detection of disease.
- Analyzing and engineering biomolecules for drug development.
- Understanding and countering changes in the environment that facilitate disease in humans and animals.
- Modeling disease progression and testing possible countermeasures to prevent epidemics.
- Recognizing potential downstream problems such as social unrest caused by biologically driven natural or manmade disasters (such as the destruction of a nation's agriculture).
- Integration of all of the above areas into comprehensive *biosurveillance*

Big Data

- Designed robotic high-throughput sequencing systems to support worldwide pathogen monitoring and enable rapid, coordinated response.
- Created 'Next Gen' DNA Sequencing and Analysis Pipeline for rapid sequence determination and analysis of biothreat/ public health pathogens.
- LANL Sequedex permits ultra-fast analysis of metagenomic sequence data for biosurveillance.
- Applied expertise in pathogen environmental genomics and

Detection and Diagnostics

- Developed hundreds of novel antibodies against tuberculosis antigens
- Developed a field-ready optical biosensor that detects protein toxins and biological pathogens such as influenza, anthrax, tuberculosis and E. coli.
- Created the world's first Portable Acoustic Cytometer that can perform high-throughput screening of possible new drugs, as well as cancer markers and infectious agents
- Developed LANL ProSig and ThermonucleotideBLAST algorithms allows for design of genetic-based detection assays for biodetection and bioforensics.
- Optimizing pathogen detection efforts by predicting bacterial adherence to environmental surfaces based on bacterial parameters such as hydrophobicity and virulence
- Validated detection assays to keep our nation safe from bioterror attacks
- Developed completely general discovery and detection platforms for early markers of disease.
- Developed non-intrusive optical spectroscopy-based diagnostic technique for cervical dysplasia—a condition that can lead to cancer.

Mechanistic Modeling

- Developed EPiSimS, an agent-based simulation engine designed to help assess disease prevention, intervention, and response strategies (Mathematical and computational epidemiology)
- Invented EpiCast, an epidemiological forecasting simulation model that can model potential bioterrorist attacks to help decision makers formulate effective countermeasures
- LANL researchers published a study using sequence analysis as a ground-truth to inform epidemiological spread of HIV in the context of an agent-based model
- Led an extensive epidemiology study for the Department of Homeland Security during the 2009 influenza pandemic to help inform decisions about how to use therapeutics and what the potential benefit (if any) would be from social distancing measures and restrictions.

Countermeasures and Therapeutics

- Designed antimicrobial proteins that rapidly eliminate bacteria from infected sites in plants and humans
- Developed chelators for radioisotope delivery systems that have applications in medical imaging and in vivo cancer therapy

- Working to understand the viral factors that facilitate transmission of HIV infection to develop preventative approaches, including possible vaccines, to curtail this epidemic. Created a new strategy for vaccine development using mosaic proteins —proteins that represent the best consensus when working with highly variable pathogens such as HIV. Mosaic proteins were used to make an HIV vaccine that is currently in a Phase 1 human trial.
- Using mosaic proteins for other vaccines, such as one against the Ebola virus"
- Performed large-scale molecular simulations of molecular machines to identify new antibiotic targets. Such understanding could help scientists develop new antibiotics to battle "superbugs" such as MRSA (methicillin-resistant Staphylococcus aureus) infections, as well as engineered strains of anthrax and plague. Also performed the first structural study of an entire long non-coding RNA, a class of molecules that play key roles in cancer and epigenetics.
- Developed genomic screens using RNAi to identify host proteins targeted by Yersinia bacteria—the successful use of this could lead to these screens being used to ascribe function to previously uncharacterized genes. A better understanding of host-pathogen interactions also has the potential to enable earlier (pre-symptomatic) detection and/or the development of more effective therapeutics.

Capabilities

Bioinformatics and Analytics	Patrick Chain
Biophysics	Jim Werner
Computational Modeling	Sara Y. Del Valle
Detection and Diagnostics	Basil Swanson
Environmental Microbiology	Cheryl Kuske
Epidemiology	Ben McMahon
Genome Technologies	Tracy Erkkila
Molecular Recognition and Design	Andrew Bradbury
Pathogen Databases	Ben McMahon
Pathogen Science	Elizabeth Hong-Geller
Protein Engineering	Geoff Waldo
Structural Biology	Tom Terwilliger

LANL Facilities and Resources

- Pathogen Research Databases: Los Alamos has in place extensive databases of genomic sequences for HIV, hepatitis C, hemorrhagic fever viruses, influenza, oral pathogens (both bacterial and viral), and bacteria and viruses responsible for sexually transmitted diseases. These data enable advanced bioinformatics analysis and rapid signature identification of various pathogen strains.
- High-Throughput Gene Cloning and Protein Production Facility: This facility serves the Tuberculosis Structural Genomics Consortium, the Integrated Center for Structure and Function Innovation, and an NIH project to select antibodies against every human protein. LANL scientists collaborate with various universities and other national laboratories to better-understand how proteins work, as these are considered the "machines of life."
- Los Alamos Molecular Recognition Alliance: The objective of this alliance is to develop antibodies and other "affinity reagents" to combat diseases. Los Alamos

has developed reagents that counter cholera, plague, anthrax, influenza, and hantavirus.

- **National Flow Cytometry Resource:** For over 30 years LANL has been a leader in the development and use of flow cytometry. This resource uses flow cytometry to analyze bacteria, viruses, infected host cells, and other particles. These techniques can be used to identify microbes, perform bacterial fingerprinting and forensics, and isolate cancer cells.
- **Protein Crystallography Station**: Scientists at this facility investigate the structure of proteins, biological polymers, and membranes. To conduct such investigations, scientists use a combination of x-ray and neutron crystallography, protein expression and purification, isotopic labeling, structural enzymology, enzyme kinetics, and molecular biology.
- Protein Structure Determination: Multiple facilities at LANL provide capabilities in NMR, and X-ray and neutron diffraction techniques to perform groundbreaking work in new drug-design methods through advanced understanding of protein structures and their functions.
- **Advanced Computing Resources:** Access to high-performance computing allows the use of rapid and specialized analysis tools for phylogenetic characterizations (Sequedex), metagenomic assembly, high throughput annotation, evolutionary modeling, and disease epidemiological modeling.
- Los Alamos Genome Center: Coupled with our mission to serve the JGI, the Genome Center houses all of the newest sequencing technologies to deliver JGI projects as well as to many other sponsors, primarily focusing on sequencing critical pathogens and near neighbors, computational finishing and bioinformatics characterization of these pathogens, database and web services for pathogen genome comparisons, metagenome sequencing and analysis for pathogen discovery and biosurveillance.
- **Joint Genome Institute (JGI)**: Los Alamos was one of the founding partners in the DOE-JGI over 10 years ago. Los Alamos scientists continue to contribute scientifically to in high-throughput genome finishing and analysis in support of DOE missions in energy, bioremediation, and carbon sequestration. Work includes developing assembly algorithms for sequence improvement of microbial genomes, and advanced bioinformatics analysis of metagenomic communities.

Sponsors, Funding Sources, or Agencies

- National Institutes of Health (NIH)
- National Institute of Allergy and Infectious Diseases (NIAID)/NIH
- Center for HIV/AIDS Vaccine Immunology
- Department of Homeland Security (DHS)
- Defense Threat Reduction Agency (DTRA)/DoD
- United States Department of Agriculture (USDA)
- Citrus Research Board
- Los Alamos Laboratory Directed Research and Development (LDRD)

Awards

- 2012 R&D 100 Award for Sequedex software which can rapidly analyze and compare genomic sequence data to identify infectious diseases
- Reagentless Optical Sensor 2004 FLC Award

- Benchtop Optical Biosensor 2011 FLC Award